TOXICITY SUMMARY AND READ-ACROSS
1,1,1,3,3,3-Hexafluoro-2-methoxypropane (HFMOP)

Executive Summary
1,1,1,3,3,3-Hexafluoro-2-methoxypropane (HFMOP), CAS No. 13171-18-1, is a substance which possesses low acute toxicity and is expected to exhibit low chronic toxicity. HFMOP is not expected to be mutagenic, is not listed as a carcinogen and is not a sensitizer. Reproductive or developmental effects should not be a concern at concentrations that would not otherwise cause adverse effects. HFMOP is expected to have relatively low aquatic toxicity and although not expected to be readily biodegradable is not expected to bioaccumulate. Releases to the environment are expected to ultimately partition mostly into air without impact on the ozone layer and with low global warming potential.

HFMOP Toxicity Testing Results

Acute Oral
An acute oral (gavage) toxicity test (OPPTS 870.1100) was conducted with HFMOP, in rats. A single limit dose of 5000 mg/kg HFMOP was administered to one animal, then two others. There was no mortality or clinical signs reported (PSL 46318, 2017). The oral LD_{50} is greater than 5000 mg/kg bw in rats.

An initial limit dose of 5000 mg/kg was administered to one healthy female rat by oral gavage. Due to the absence of mortality in this animal, two additional females received the same dose level, simultaneously. Since these animals survived, no additional animals were tested. Females were selected for the test because they are frequently more sensitive to the toxicity of test compounds than males. All animals were observed for mortality, signs of gross toxicity, and behavioral changes at least once daily for 14 days after dosing. Body weights were recorded prior to administration (initial) and again on Days 7 and 14 (terminal) following dosing. Necropsies were performed on all animals at terminal sacrifice.

All animals survived test substance administration, gained body weight, and appeared active and healthy during the study. There were no signs of gross toxicity, adverse clinical effects, or abnormal behavior. No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period.

Acute Dermal
An acute dermal toxicity test (OPPTS 870.1200) was conducted with HFMOP, in rats. A single topical application of 5000 mg/kg HFMOP was applied to 10 animals, for 24 hours. There were no mortalities or clinical signs reported (PSL 46319, 2017). The dermal LD_{50} is greater than 5000 mg/kg bw in rats.

An acute dermal toxicity test was conducted with rats to determine the potential for 1,1,1,3,3,3-Hexafluoro-2-methoxypropane (HFMOP) to produce toxicity from a single topical application. Under the conditions of this study, the single dose acute dermal LD_5o of the test substance is greater than 5000 mg/kg of body weight in male and female rats.

Five thousand milligrams of the test substance per kilogram of body weight was applied to the skin of ten healthy rats for 24 hours. The animals were observed for mortality, signs of gross toxicity, and behavioral changes at least once daily for 14 days. Body weights were recorded prior to application (initial) and again on Days 7 and 14 (terminal). Necropsies were performed on all animals at terminal sacrifice.

All animals survived test substance administration, gained body weight, and appeared active and healthy during the study. There were no signs of gross toxicity, dermal irritation, adverse clinical effects, or abnormal behavior. No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period.

Acute Inhalation

An acute inhalation toxicity test (OPPTS 870.1300) was conducted with HFMOP, in rats. A single exposure, nose-only, of 5.19 mg/L HFMOP was given to 10 animals, for 4 hours. There were no mortalities or clinical signs reported after 14 days (PSL 46320, 2017). The inhalation LC_{50} is greater than 5.19 mg/L in rats.

An acute inhalation toxicity test was conducted with rats to determine the potential for 1,1,1,3,3,3-Hexafluoro-2-methoxypropane (HFMOP) to produce toxicity from a single exposure via the inhalation (nose-only exposure) route. Under the conditions of this study, the single exposure acute inhalation LC_{50} of the test substance is greater than 5.19 mg/L in male and female rats.

After establishing the desired generation procedures during the pre-test trials, ten healthy rats (5/sex) were exposed to the test atmosphere for 4 hours. Chamber concentration and particle size distributions of the test atmosphere were determined periodically during the exposure period. The animals were observed for mortality, signs of gross toxicity, and behavioral changes at least once daily for 14 days following exposure. Body weights were recorded prior to exposure (initial) and again on Days 1, 3, 7, and 14 (terminal). Necropsies were performed on all animals at terminal sacrifice.

The gravimetric chamber concentration was 5.19 mg/L. The average mass median aerodynamic diameter was estimated to be 1.91 µm based on graphic analysis of the particle size distribution as measured with a l ACFM Andersen Ambient Particle Sizing Sampler with an average geometric standard deviation of2.08. All animals survived exposure to the test atmosphere and gained body weight during the study. Following exposure, four animals were hypoactive and all animals exhibited irregular respiration and/or ano-genial staining. However, all animals recovered by Day 2 and appeared active and healthy for the remainder of the 14-day observation period. No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period.

Eye Irritation

A primary eye irritation assay (OPPTS 870.2400) was conducted with HFMOP, in rabbits. A single instillation of HFMOP was introduced into one eye of three rabbits (PSL 46321, 2017). HFMOP was considered to be practically non-irritating to the eye.

One-tenth of a milliliter of HFMOP was instilled into the right eye of three healthy rabbits. The left eye remained untreated and served as a control. Ocular irritation was evaluated by the Draize method of scoring (Draize, Woodard, & Calvery, 1944).

One hour after test substance instillation, minimal conjunctivitis was noted for one treated eye, which cleared by 24 hours. There was no corneal opacity or iritis observed in any treated eye during this study.

Skin Irritation

A primary skin irritation assay (OPPTS 870.2500) was conducted with HFMOP, in rabbits. A single topical dose of HFMOP was applied to the skin of three rabbits (PSL 46322, 2017). HFMOP was considered to be slightly irritating to the skin.

Five-tenths of a milliliter of HFMOP was applied to the skin of three healthy rabbits for 4 hours. Following exposure, dermal irritation was evaluated by the Draize method of scoring (Draize, Woodard, & Calvery, 1944.

Within 30-60 minutes of patch removal, two treated sites exhibited very slight erythema and very slight edema. All animals were free of dermal irritation by 48 hours.

Skin Sensitization

A dermal sensitization assay (OPPTS 870.2600) was conducted with HFMOP, guinea pigs. HFMOP was topically applied to 20 test guinea pigs (PSL 46323, 2017). HFMOP was not considered to be a contact sensitizer.

The neat test substance was topically applied to twenty healthy test guinea pigs, once each week for a three-week induction period. Twenty-seven days after the first induction dose, a challenge dose of HFMOP, at its highest non-irritating concentration (HN1C, determined in the preliminary irritation screen to be 100%), was applied to a naive site on each guinea pig. A naive control group (ten animals) was maintained under the same environmental conditions and treated with the test substance at challenge only. Approximately 24 and 48 hours after each induction and challenge dose, the animals were scored for erythema.

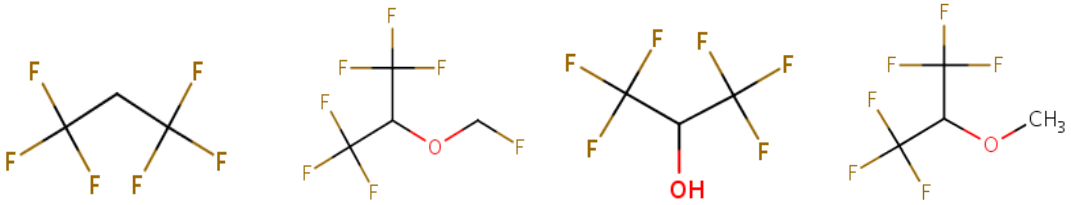
Based on the results of this study, the test substance is not considered to be a contact sensitizer. The positive response observed in the historical positive control validation study with alpha- hexylcinnamaldehyde, 95% (HCA) validates the test system used in this study.

Read-Across

Due to the limited amount of data on HFMOP, a Data Matrix (see below) was constructed in order to compare the health and environmental effects of three substances with similar structures; two being liquids and one being a gas at room temperature.

HFMOP (1,1,1,3,3,3-Hexafluoro-2-methoxypropane), HFP (1,1,1,3,3,3-Hexafluoropropane), HFIP (1,1,1,3,3,3-Hexafluoroisopropanol) and HFFMOP (1,1,1,3,3,3-Hexafluoro-2-(fluoromethoxy)propane all are 1,1,1,3,3,3-Hexafluoro substances of similar molecular weights and share several predicted and actual data similarities.

HFP HFFMOP HFIP HFMOP



Especially related are the three liquids, HFFMOP, HFIP and HFMOP, but HFP has been included because it has gone through a WEEL evaluation and has a published WEEL value of 1000 ppm. Since HFFMOP (also known as Sevoflurane) is used as an anesthetic, and both HFFMOP and HFMOP partition readily to the air, particular attention to their relatedness might be of value when making read-across arguments or looking for similar well-known substances for risk assessment purposes. Please review the Data Matrix below for more information.

Data Matrix

All values were measured experimentally unless otherwise noted.

Chemical Name:	HFP CAS: 690-39-1 (Read-Across)	HFFMOP CAS: 28523-86-6 (Read-Across)	HFIP CAS: 920-66-1 (Read-Across)	HFMOP CAS: 13171-18-1 (PMN Substance)
PYSICOCHEMICAL PROPERTIES:				
Molecular Weight	152.04	200.05	168.04	182.07
Physical State at Room Temp.:	Gas	Liquid	Liquid	Liquid
Melting Point (°C)	-103 (2)	0 - 25 (5)	-2.0 (3)	Not available
Boiling Point (°C)	-2 (2)	58.6 (5)	59 (3)	50 (9)
Specific Gravity	N/A	1.5 (5)	1.46 (3)	1.38 (9)
Vapor Pressure kPa @ 20 °C	249 (2)	20.93 (5)	15.06 (3)	36.1 (9)
Water Solubility (mg/L)	724 (2)	1406 (1)	7770 (1)	1400 (9)
Flash Point (°C)	Non-flammable (2)	Not determined	Not determined	Non-flammable
Partition Coefficient Kow)K_{ow})	2.64 (1)	1.75 (1)	1.11 (1)	1.81 (1)
Auto flammability (°C)	No data	No data	No data	No data
Viscosity (mPa s)	No data	No data	No data	No data
ENVIRONMENTAL FATE and PATHWAY:				
Biodegradation	Not readily biodegradable (2)	Not readily biodegradable (1)	Not readily biodegradable (3)	Not readily biodegradable (1)
Bioaccumulation (Log BCF)	1.413 (1)	0.6598 (1)	0.762 (1)	0.859 (1)
Adsorption / Desorption (Log Koc)	2.53 (2)	1.89 (1)	1.43 (1)	1.93 (1)
Henry's Law Constant (atm-m3/mole)	3.46 (1)	0.187 (1)	0.004 (1)	0.009 (1)
Atmospheric Half-Life (Days) [12-hr day; 1.5E6 OH/cm3]	2,271 (1)	157.75 (1)	61.391 (1)	66.165 (1)
Global Warming Potential (100 yr.)	9,810 (8)	216 (8)	195 (8)	27 (8)
ENVIRONMENTAL TOXICITY:				
Acute toxicity to fish LC_{50} (mg/L)	292 (2)	276.9 (1)	873.56 (1)	222.9 (1)
Acute toxicity to aquatic invertebrates (Daphnia, LC_{50}), mg/L	19.79 (1)	153.6 (1)	456.79 (1)	124.3 (1)

Chemical Name:	HFP CAS: 690-39-1 (Read-Across)	HFFMOP CAS: 28523-86-6 (Read-Across)	HFIP CAS: 920-66-1 (Read-Across)	HFMOP CAS: 13171-18-1 (PMN Substance)
Toxicity to aquatic plants (Green Algae, EC_{50}), mg/L	186 [2]	103.9 [1]	242.04 [1]	86.03 [1]
MAMALIAN TOXICITY:				
Acute oral (rat), mg/kg-bw	No data	10,800 [5]	No data	>5,000
Acute inhalation (rat), ppm	457,000 (4hr) [2]	28,800 (3hr) [5]	1974 (4hr) [4]	7540 (4hr)
Acute dermal (rabbit), mg/kg-bw(LD_{50})	No data	No data	No data	>5000
Specific Target Organ Toxicity - Single Exposure (STOT-SE)	May cause drowsiness or dizziness at high concentrations.			
Specific Target Organ Toxicity - Repeated Exposure (STOT-RE)	Negative [2]	Negative [5]	Negative [3]	No data
Genetic toxicity	Negative [2]	Negative [5]	Negative [3]	No data
Carcinogenicity	Not listed	Not listed	Not listed	Not listed
Reproductive toxicity	Negative [2]	Note 1	Note 2 [3]	No data
Developmental toxicity	Negative [2]	Note 1	Note 2 [3]	No data
Sensitization	No data	No data	Negative [3]	Not a skin sensitizer
Skin irritation / corrosion	No data	Slightly irritating [5]	Skin Corr. 1A [3]	Slightly irritating
Eye irritation / corrosion	No data	Severe eye irrit. [5]	Eye Dam. 1 [3]	Practically non-irritating

Note 1: Epidemiological studies suggest higher than normal incidences of problem pregnancies (particularly spontaneous abortions) among exposed personnel to various anesthetic gases. [6] FDA Pregnancy risk category B: No Evidence of Risk To Humans. [7]

Note 2: The registrant classified the substance as GHS Reproductive/Developmental Toxicity Category 2. However, it is unclear whether the effects noted are an intrinsic property of the test substance or instead related to maternal toxicity caused by the anesthetic action of the test substance and evident at the highest dose tested. [3]

References:

[1] USEPA EPIWin or ECOSAR

[2] ECHA (2018a). European Chemicals Agency. ECHA Chem Database. Information on Registered Substances. EC number 425-320-1, 1,1,1,3,3,3-Hexafluoropropane. Last updated 21 April 2017. Available at https://echa.europa.eu/registration-dossier/-/registered-dossier/18979

[3] ECHA (2018b). European Chemicals Agency. ECHA Chem Database. Information on Registered Substances. EC number 213-059-4, 1,1,1,3,3,3-hexafluoropropan-2-ol. Last updated 23 April 2017. Available at https://echa.europa.eu/registration-dossier/-/registered-dossier/10316

[4] National Technical Information Service. Vol. OTS0571423

[5] Supplier Safety Data Sheets for Sevoflurane

[6] DHHS (2007). U.S. Department of Health and Human Services. Center for Deseae Control and Prevention. National Institute for Occupational Safety and Health. Waste Anesthetic Gases Occupational Hazards in Hospitals. Publication No. 2007-151. September 2007.

[7] US NIH (2012). US Natl Inst Health; DailyMed. Current Medication Information for ULTANE (sevoflurane) liquid (May 2011). Available from, as of June 9, 2012: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=4c6e76bc-c964-4955-e0a3-511d3386a9cc

[8] 40 CFR Appendix Table A-1 to Subpart A of Part 98, Global Warming Potentials

[9] A. Sekiya, S. Misaki. Journal of Flourine Chemistry. Table 1. 101 (2000) 215-221.